REMARKS

Claims 1-100 were pending in the application. Previously withdrawn claims 1-75 and 82-100 have now been cancelled. New claims 101-119 have been added. Pending claims 76-81 have been finally rejected. Specifically, all claims were rejected under 35 USC 101 as being directed to non-statutory subject matter. In addition, all claims were rejected as being anticipated by US Patent Application 2001/0051855 naming Wang et al. as inventors. These rejections will be addressed below in turn.

The independent claims (claims 76 and 79) have been amended to recite that "the data characterizing the training set" comprises "activity and a nucleotide sequence for each protein variant in the training set." Support for these amendments is found at page 12, line 31 to page 13, line 20, for example. The independent claims have also been amended to recite that the sequence activity model is a "computational algorithmic" model. Support for this amendment is found at page 13, lines 21-26, and page 20, line 32 to page 21, line 8, for example. The independent claims have been further amended to recite use of a "reference nucleotide sequence." Support for this amendment is found at page 15, lines 6-8, for example. Further, independent method claim 76 has been amended to recite generating particular protein variants. Support for this amendment is found at various places in the specification. Finally, computer program product claim 79 has been amended to recite code for generating ranked lists of "nucleotide positions and/or the nucleotide types at specific positions in the nucleotide sequence." Support is found at various points in the application such as page 23, lines 3-21. Suitable computer systems that generate and store such results are described beginning at page 80.

New dependent method claims 101-108 have been added to further specify certain embodiments of the invention. These claims find support throughout the specification. As examples, claims 105 and 106 find support at page 29, lines 24-25. In addition, claim 107 finds support in the specification at page 29, lines 25-29. Further, claim 108 finds support at page 30, lines 24-25.

A new claim set (claims 109-119) has also been added. This claim set finds support in the original claim set and its amendments along with the disclosure found at page 30, lines 21-28.

Claim Rejections 35 USC § 101

Applicants understand the Examiner's position in this rejection as requiring some type of transformation in the claims. The Applicants do not believe that either the controlling case law

or the current PTO guidelines require such transformation. This position was persuasively set forth in response to the previous rejection.

However, to expedite prosecution, Applicants have amended independent method claim 76 to recite generating one or more protein variants. Further, Applicants have amended independent computer program product claim 79 to recite that a result (a ranked list of nucleotide types or positions) can be generated in a computer system. Such list represents a physical transformation of algorithmic operations to a resulting list that would be stored, at least temporarily. Therefore, withdrawal of the rejections of these claims under section 101 is respectfully requested.

The Rejections under 35 USC § 102

All pending claims were rejected as anticipated by US Patent Application 2001/0051855 naming Wang et al. as inventors. This patent application describes procedures for determining "structurally tolerant" residues in a sequence. Mutations of the structurally tolerant residues are relatively unlikely to produce inactive sequences during directed evolution procedures. The application proposes directed evolution techniques in which residues identified as structurally tolerant are selectively mutated. Various techniques are identified for identifying structurally tolerant residues. The principal technique involves calculation of a sequence's fitness based on its conformational energy. This approach is emphasized throughout the Wang et al. application (see e.g., paragraphs 115 to 118) and is the basis for all examples presented in the application (see Section 6).

As explained in the Applicants' previous response no "expressions" or "models" employed in the Wang et al. reference were developed using a training set, but were instead developed *a priori* from general knowledge about amino acid residue structures and energetic interactions between side chains.

It does not appear that the Final Office Action addresses this position directly. Rather, at paragraphs 19-21 of the Action, the Examiner seems to be suggesting that the claims do not adequately specify the concept of a training set:

> 19. Applicants argue . . . that the teachings of Wang et al. do not develop "a sequence activity model" from "a training set of a protein variant library" and that the expressions of Wang et al. are not "developed from a *training set*."
>
> 20. In response to applicant's argument . . . , it is noted that the features upon which applicant relies are not recited in

> the rejected claim(s). Independent claims 76 and 79 recite "from the data, developing a sequence activity model," (claim 76, line 7) wherein the data is data "characterizing a training set of a protein variant library" (claim 76, line 4). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. . . . .

Applicants respectfully dispute the contention that the relevant features are not recited in the rejected claims. The claim language provides a sufficient logical connection to distinguish the prior art: (1) a sequence activity model is developed from data, and (2) the data "comprises activity and a nucleotide sequence for each protein variant in the training set." As explained clearly, the Wang et al. makes no such use of a training set.

The Examiner also states in paragraph 22 of the Action that

> Furthermore, a definition of a "training set" is not provided in the specification, while a possible example (specification, page 13, lines 2-6) includes training set data with "a complete or partial residue sequence" and/or "an activity" value which fits the concept of providing a parent sequence to generate mutant polymers that are then selected based on properties of interest and made into the parent sequence in the next evolutionary step (paragraph 0023). As reiterated in the above rejection, this reads on the claim 76, line 4, limitation of "receiving data characterizing a training set."

Considering the clear claim limitations, it is difficult to discern exactly what the Examiner is getting at here. First, the general concept of a training set in model development is very well known in the art. Second, the specification uses the term "training set" clearly and consistently at many locations, so there should be no question about its meaning in the described embodiments. Third, the clear claim language indicates that (1) the training set is "of a protein variant library" and (2) data used to develop a sequence activity model "comprises activity and a nucleotide sequence for each protein variant in the training set." This is all that is needed to understand the role of the training set in the claimed invention and to distinguish the cited Wang et al. reference.

As explained in the specification, the activity of a protein variant can be obtained by screening and assays. Examples include catalytic activity, resistance to pathogens and/or toxins, therapeutic activity, toxicity, and thermal stability. See page 13, lines 13-25, for example. A nucleotide sequence simply includes the identity of particular nucleotides or codons at particular locations in a nucleic acid.

A numerical/symbolic example may help explain the concept of training set data comprising "activity and a nucleotide sequence for each protein variant in the training set." The Examiner's attention is directed to the example spanning pages 24-26 where activity and nucleotide sequences are provided for protein variants (members of the training set).

As pointed out Applicants' previous response, the claims have other limitations that are not suggested in the Wang et al. reference. For example, claim76 recites

> using the sequence activity model to rank positions in a nucleotide sequence and/or nucleotide types at specific positions in the nucleotide sequence in order of impact on the desired activity . . . .

As explained previously, the Examiner's reference to paragraphs 0083 and 0084 of the Wang et al. application cannot support a ranking of positions in a nucleotide sequence. However, the Examiner took issue with Applicants' argument in this regard, providing the following argument:

> In response to applicant's argument that the references fail to show certain features of applicant's invention (i.e. ranking positions of individual amino acids or nucleotides) it is noted that the features upon which applicant relies are not recited in the rejected claims(s). . . . Claim 76, step b, recites predicting activity "as a function of nucleotide types and corresponding position" in the sequence, and claim 76, step c, recites "using the sequence activity model to rank position in a nucleotides sequence and/or nucleotides types at specific position . . ." The recited limitations are not limited to the fitness of any one amino acid or nucleotide at a specific position (i.e. individual amino acids or nucleotides) and encompass determining activity for groups of nucleotides either adjacent or even separated at a specific location in a sequence.

Assuming for the sake of argument that what is ranked by the claims encompasses "groups of nucleotides either adjacent or even separated at a specific location in a sequence," this does not render the claims so broad that they read on the cited prior art. As explained previously, the Wang et al. reference does not rank any such portions of a sequence. Paragraphs 0083 and 0084 of Wang use of the term "fitness" in the context of whole sequences, not portions such as individual amino acids, nucleotides, or codons. Therefore, these paragraphs cannot suggest a ranking of positions in a nucleotide sequence.

For all of the above reasons, the cited Wang et al. reference fails to anticipate the independent claims (claims 76 and 79) as well as any of the dependent claims (claims 77, 78, 80, and 81). Withdrawal of the art rejections is respectfully requested.

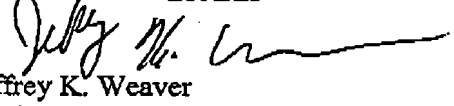
New claims 109-119 recite methods and computer program products for identifying nucleotides for variation in a nucleotide sequence in order to optimize the expression properties of the nucleotide sequence. Specifically, the variations in the nucleotide sequence are for impacting "the quantity of protein expressed." Some other features from the previously pending claims are recited in these claims. For at least the reasons set forth above, it is respectfully submitted that new claims 109-119 are patentable over the cited art.

Conclusion

Applicants believe that all pending claims are allowable and respectfully request a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

If any fees are due in connection with the filing this Response, the Commissioner is hereby authorized to charge such fees to Deposit Account 500388 (Order No. MXGNP004X1).

Respectfully submitted,
BEYER WEAVER LLP



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